Comments on

DRAFT

Report on Carcinogens

Substance Profile for

Glass Wool Fibers (Respirable) as a Class

For presentation at the
NTP Board of Scientific Counselors (BSC) Meeting
Peer Review of Draft Substance Profile
For the 12th Report on Carcinogens
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Table of Contents

1. Summary

Decisions on listing or not listing substances in the Report on Carcinogens (RoC) must be based on scientific information on the specific chemical or the substances under review. In the case of specific chemicals, whose physical and chemical properties never change, all the scientific evidence developed, irrespective of when it was developed, is relevant and can be synthesized and integrated to evaluate the carcinogenic hazard of the chemical. Unlike a specific chemical, glass fibers represent a diverse class of substances that have in common two characteristics; they have the composition of glass and the shape of fibers. A large number of different fibers have been produced over the years with the composition and size varied to maximize the utility of the fibers for specific application. New research conducted largely over the past two decades provides a basis for sub-dividing glass fibers into two categories: (a) Special Purpose Glass Fibers, and (b) Insulation Glass Fibers. These two broad categories of glass fibers are purposefully produced to have different composition and size characteristics matched to their intended use. Most importantly, new scientific information developed during the past two decades is now being used to guide the production and use of glass fibers used for insulation purposes to ensure that these products are not biopersistent and, thus, do not pose a carcinogenic hazard. Because of its recent origin that information was not considered in preparing the Substance Profile for Glass Wool (Respirable Size) listed in the Seventh Annual Report on Carcinogens (RoC) (1994) and subsequent RoCs.

It is noteworthy that the International Agency for Research on Cancer (IARC) in 2001 determined that new scientific evidence provided a basis for making different classifications for different types of man-made vitreous fibers. This was a shift from 1988 when IARC lumped all man-made vitreous fibers together. IARC (2002) determined that special purpose glass fibers and refractory ceramic are *"possibly carcinogenic to humans"* based on *insufficient human epidemiological evidence and sufficient evidence of carcinogenicity in animals*. In a parallel action, IARC determined that insulation glass wool, continuous glass filament, rock (stone) wool and slag wool fibers, based on a lack of epidemiological and toxicological evidence, are <u>not</u> *classifiable to as to carcinogenicity to humans*. The IARC findings were one factor motivating the North American Insulation Manufacturers Association to request that NTP re-evaluate the listing in the 11th RoC of "Glass Wool (Respirable) Size, as reasonably anticipated to be a human

carcinogen" for glass wool fibers (NTP 2004), a continuation of the listing in the 7th RoC (Hadley and Mentzer, 2004).

An NTP appointed Glass Wool Fibers Expert Panel, that included 9 individuals with broad expertise relevant to evaluating the carcinogenic hazard of glass fibers, met on June 9-10, 2009 and was charged (1) to apply the RoC listing criteria to the relevant scientific evidence and make a recommendation regarding its listing status (i.e. *known to be a human carcinogen, reasonably anticipated to be a human carcinogen*, or not list) in the 12th RoC and (2) to provide a scientific justification for the recommendation. As background for its deliberations, the NTP Expert Panel was provided the document – "Draft – Report on Carcinogens Background Document for Glass Wool Fibers" (NTP, 2009a) and written public comments provided by representatives of the insulation glass fiber industry (Mentzer, 2009; Bauer, 2009; Marsh et al. 2009; Hesterberg et al. 2009; Hadley, 2009; Donaldson, 2009). These written comments summarized the results of two decades of research with appropriate supporting citations to numerous papers published in the peer reviewed scientific literature. The NTP Expert Panel (Kelsey, 2009a) provided useful recommendations for revising the Draft Report which would become the "Final Report on Carcinogens Background Document for Glass Wool Fibers, September 9, 2009" (NTP, 2009b).

The Expert Panel (Kelsey, 2009b) recommended to the NTP that separate cancer hazard classifications be provided for glass wool fibers and special purpose fibers. Specifically, the Expert Panel, by a vote of 8 yes and 0 no, recommended that "glass wool fibers, with the exception of special fibers of concern (characterized physically below) should not be classified as known to be a human carcinogen or reasonably anticipated to be a human carcinogen." The Expert Panel, by a vote of 7 yes, 0 no and 1 abstention, "based on sufficient evidence of carcinogenicity in well-conducted animal inhalation studies, that special purpose glass fibers with the physical characteristics as follows – longer, thinner, less soluble fibers (for example, ≥ 15 μm length with a K_{dis} of ≤ 100 mg/cm^2/h) are *reasonably anticipated to be a human carcinogen* for the listing status in the RoC."

Subsequent to receipt of the Expert Panel's recommendations, assuming the NTP followed its established procedures (NTP, 2010a), two internal review groups were convened to offer recommendations on an initial listing status. These two groups were the (1) Interagency Scientific Review Group (ISRG), and (2) NIEHS/NTP Scientific Review Group (NSRG). The

specific participants nor their credentials have not been public and the meetings of these internal review groups were closed to the public. The NTP process (NTP, 2010a) calls for the development of a draft substance profile with a listing recommendation for each candidate substance based on the listing recommendation of the Expert Panel, NSRG and the ISRG and public comments. The "Draft RoC Substance Profile for Glass Wool Fibers (Respirable) as a Class" (NTP, 2010b) provides a preliminary recommendation that does not follow the recommendations of the Expert Panel and the Public Comment. Apparently with deference an independent assessment by the NTP staff, the NSRG and/or the ISRG, the Draft Substance Profile provides a preliminary recommendation for the continued listing of "Glass Wool Fibers (Respirable) as a Class" as *"reasonably anticipated to be a human carcinogen."*

This proposed preliminary recommendation ignores a substantial body of scientific evidence that strongly supports the science-based recommendations of the NTP Expert Panel to list Special Purpose Fibers as *"reasonably anticipated to be a human carcinogen"* and to not list glass wool fibers. The Draft Substance Profile Preliminary Recommendation is apparently justified by the NTP by lumping together (a) the animal evidence from well-conducted studies for Special Purpose Fibers showing some evidence of carcinogenicity with (b) glass wool insulation fibers for which there is a lack of evidence of carcinogenicity in well-conducted long-term inhalation studies. For neither type of fiber was there sufficient human evidence of carcinogenicity. The preliminary recommendation is simply a wrong-minded, non-scientific approach. Following this line of argument, it could be concluded that because some chemicals are human carcinogens it could be argued that based on lumping them all together "Chemicals as a Class" should be listed as Human Carcinogens.

The proposed preliminary recommendation, if not altered, removes the incentive for either private industry or the government to sponsor any research that seeks to create safer products. It also is an injustice to the Public that looks to the RoC for science-based information that will guide decisions on purchasing and using products. The potential dilemma is especially profound as the Public makes decisions or whether to use or not use glass wool fiber insulation products to help conserve energy as part of a national energy strategy. Moreover, the failure to recognize that glass fibers can be classified as to potential carcinogenic hazard based on their physical characteristics or the results of short-term biopersistence studies will perpetrate a requirement to continue using large numbers of animals in long-term inhalation studies to verify

an absence of carcinogenic effects for each glass wool fiber being considered for introduction to the market. This unintended consequence is not in keeping with current efforts by many parties, including the NIEHS, NTP, and the Glass Fiber Industry to reduce the number of animals needed in studies to demonstrate the safety of new products.

We urge the Board of Scientific Counselors to recommend to the NTP Management and Staff that the science-based advice of the NTP Expert Panel be followed in finalizing the 12th RoC. A science-based decision on glass wool fibers used for insulation purposes will send the appropriate signal to scientist, industry and the government that when safer products are developed, the NTP will acknowledge the scientific evidence in making listing or de-listing decisions for inclusion in future RoC.

2. Context for Listing/De-Listing Decisions

The National Toxicology Program Report on Carcinogens serves a valuable public service role informing government agencies, private industry and, most importantly, the American Public as to the potential carcinogenic hazards of substances they may encounter in the course of their daily activities. The listing of substances in the RoC as a known *human carcinogen or reasonably anticipated to be a human carcinogen* has significant impact as to how many of the substances may be regulated by various government agencies. Moreover, the listing and associated label of potential carcinogenic hazard has impact on the use of these substances by the public. It is also important to recognize the positive impact associated with a substance being evaluated and not listed in the RoC, consumers have greater confidence that products containing unlisted substances are safe if used for their intended purpose. It is clear that the decision to list or not list a substance has major societal impact.

The vast majority of substances evaluated for listing in the RoC are specific chemicals, for example, formaldehyde and benzene. All chemicals have very specific physical and chemical properties such as their molecular structure, solubility, boiling point, etc., properties that never change. Obviously, what is known about the biological properties and toxicological effects of specific chemicals does change over time with advances in the fields of biology and toxicology, as new methods are introduced and as the body of scientific knowledge expands on specific chemicals.

Only a few substances, such as glass wool fibers, considered for listing in the RoC are not specific chemicals. Glass wool fibers represent an extraordinarily broad range of materials that

share the common characteristics of (a) being vitreous or composed of glass, i.e. oxides of silicon or closely related elements that can be melted and quenched into a glassy state and (b) having a fiber shape, i.e. a length to width ratio of at least 3 to 1. The specific chemical composition of glass fibers and their size and other physical properties can be altered by changing the chemical composition of the starting ingredients and the manufacturing process used to produce the glass fibers. The ability to make different kinds of fibers allows industry to produce fiber glass products that have properties matched to their intended use. Some special purpose fibers may be used in highly specialized applications. These special purpose fibers may be produced in modest quantities, be expensive to produce and command a premium price in the market place. The vast majority of glass fibers produced today are typically used for insulation purposes. The wide usage of glass fibers in insulation products relates to their desirable insulation properties and the ability of industry to produce and market them at a reasonable cost.

During the last two decades, the fiber glass industry has conducted in-house research and sponsored externally substantial research, the results of which provide a sound scientific basis for producing products that have desirable insulation properties and do not pose a carcinogenic hazard. The results of that research has been published in peer-reviewed journals, most appearing in print after the Seventh Annual Report on Carcinogens (1994) was prepared. A key finding of the recent research was the demonstration that glass fibers with high *in vitro* fiber dissolution rates had low biopersistence and, in turn, when evaluated in well-conducted inhalation studies did not produce cancer even with long-term exposures to high concentrations of respirable glass fibers. This provides a sound scientific basis for using physical characterization data and the results of short-term biopersistence studies as indicators of potential carcinogenic hazards. This has an associated positive impact of the number of animals needed for safety evaluation studies compared to continuing the use of inhalation bioassays that require the use of large numbers of animals.

The scientific information developed since the Seventh Annual Report on Carcinogens (1994) was prepared provides a sound scientific basis for revising the listing, "Glass Wool Fibers (Respirable) as a Class" – *"Reasonably anticipated to be a human carcinogen,"* a listing which has appeared in each subsequent RoC. As recommended by the NTP Expert Panel on Glass Fibers, the scientific evidence now supports a listing of "Special Purpose Fibers – *"Reasonably anticipated to be a human carcinogen"* because they are generally biodurable and biopersistent,

and thus, have been shown to produce respiratory tract cancer in rodents in well-conducted inhalation studies. A large and compelling body of scientific evidence has demonstrated that biosoluble glass wool fiber used for insulation purposes are not biopersistent and not carcinogenic in well-conducted inhalation studies conducted in rodents. Thus, as recommended by the NTP Expert Panel, this category of glass wool fibers should not be listed in the RoC.

3. Evolution of Fiber Glass Products

Glass Fibers with variable physical characteristics, such as size, durability and thermal insulation properties, have found widespread applications and, thus, become valuable products. This has stimulated research and development activities to produce glass fiber products with improved characteristics matched to their intended use.

Concern for the safety of fiber glass stimulated a major research program, beginning in the late 1980s, funded by the Glass Fiber Industry, to better understand the characteristics of fibers associated with toxicity and then re-engineer production processes to produce safer products. That research effort was conducted both in-house in company laboratories and under contract in laboratories that had the specialized capability for conducting long-term, nose-only inhalation exposure studies in rodents with well-characterized aerosols of glass fibers. To help ensure the quality of the studies, external consultants experienced in aerosol science, inhalation toxicology, statistics, comparative pathology and risk assessment were involved in developing protocols and oversight of the research. Several of the consultants, Eugene McConnell and Roger McClellan, had extensive experience conducting and managing studies that conformed to the standards set by the NTP for long-term studies conducted by contractors to the NTP.

The results of that extensive research program using a wide range of well-characterized glass fibers has clearly demonstrated the key role of the dissolution characteristics of glass fibers in determining biopersistence of inhaled fiber and, in turn, the role of biopersistence of fibers in determining whether inhalation exposure to a particular type of glass fiber would or would not cause respiratory tract cancer. In short, glass fibers that are thin, long and biodurable are capable of causing respiratory tract cancers when inhaled by rodents for long periods of time with fiber concentrations that are sufficiently high. Conversely, glass fibers that were not biopersistent, even if they have diameters and length characteristics that result in their being respirable, did not cause cancer in well-conducted rodent studies.

The glass fiber industry has used the new research results as a key input to evaluating existing products, and, especially, in the development and introduction of new products, to ensure that the products do not pose a potential carcinogenic hazard. In some cases, such as with certain Special Purpose Fibers, it was determined that the chemical and physical characteristics, including solubility, could not be changed while still maintaining the desired in service characteristics of the fiber glass product. In these cases, special efforts were taken to ensure that work place exposures associated with manufacture and use of the product were held as low as practical. In 1999, the Occupational Safety and Health Administration (OSHA), trade associations representing U.S. insulation manufacturers, and insulation contractors agreed to a voluntary standard for exposure to glass fibers (OSHA, 1999; NAIMA, 1999). The Voluntary Health and Safety Partnership Program included a voluntary Permissible Exposure Level of 1 respirable fiber/cc and a commitment from manufacturers to formulate or reformulate fibers with increased biosolubility as necessary. The leadership of OSHA applauded this industry initiative.

In 1997, based on the new body of scientific information, the Commission of the European Communities (EU, 1997) established criteria for classifying and labeling synthetic vitreous fibers according to their potential hazard to human health. Specifically, the formal directive stated –

"The classification as a carcinogen need not apply if it can be shown the substance fulfills one of the following conditions:

- a short-term biopersistence test by inhalation has shown the fibers longer than 20 μm have a weighted half life less than 10 days, or
- a short-term biopersistence test by intratracheal instillation has shown that the fibers longer than 20 μm have a weighted half-time less than 40 days, or
- an appropriate intra-peritoneal test has shown no evidence of excess carcinogenicity, or
- absence of relevant pathogenicity or neoplastic change in a suitable long-term inhalation test."

Protocols have been developed matched to these criteria (Bernstein and Riego-Sintes, 1999). The adoption of this formal directive served as a major stimulus to glass fiber Manufacturers to develop, test, and, then, market synthetic glass fibers that had low biopersistence and could meet the criterion. The European Commission (EU, 1997) Directive

also had a "halo" effect in influencing the manufacture and marketing of low biopersistence and hence, safer fibers in many markets around the world. Indeed, Australia and New Zealand have already adopted similar approaches.

The IARC in 1987 conducted an in-depth evaluation of the carcinogenic potential of glass fibers and published its findings the following year (IARC, 1988). The IARC monograph (1988) classified Glass Wool (including fiber glass) as *"possibly carcinogenic to humans"* based on *"inadequate human evidence"* and *"sufficient animal evidence."* In this early evaluation, considerable weight was given to the results of intra-cavity implantation and injection studies since the inhalation studies conducted up to that time were not well-designed nor conducted to the rigorous standards introduced later. The 1988 IARC monograph did not distinguish between different sub-categories of fibers since there was not sufficient published scientific information available in 1987 to make such a distinction and provide separate cancer hazard evaluations for different types of glass fibers.

The IARC (2002) published a re-evaluation of the carcinogenic hazards of synthetic vitreous fibers, a re-evaluation stimulated by the substantial body of new information acquired since its review in 1987. The membership of the IARC Scientific Committee is listed in Appendix A. The new scientific evaluation concluded that insulation glass wool was *"not classifiable as to their carcinogenicity to humans"* based on *"inadequate human evidence"* and *"limited animal evidence."* It concluded that Special Purpose Fibers and Refractory Ceramic Fibers are *"possibly carcinogenic to humans"* based on *"inadequate human evidence"* and *"sufficient animal evidence."* The body of evidence that the IARC experts used to draw these conclusions is at the core of NTP's current re-evaluation of glass wool fibers. Additional papers on glass fibers have been published since the IARC evaluation, they provide increased scientific evidence that support the 2002 IARC conclusions and do not countermand those conclusions.

The IARC (2002) Classification has had world-wide impact. In particular, the changes in cancer hazard classification in 2002 based on new scientific information sends a strong message with regard to the development of safer products. The interest in developing safer and greener products certainly extends to the United States. The U.S. Environmental Protection Agency, one of the agencies participating in the NTP, under the leadership of Dr. Paul Anastas, the Assistant Administrator for Research and Development, has adopted a set of 12 Principles of Green Chemistry. The principles were initially stated in Green Chemistry, Theory and Practice

(Anastas and Warner, 1998). The second principle on the list is – "Design chemicals and products to be fully effective but have little or no toxicity." It is my understanding that Dr. Linda Birnbaum, in her role as Director of the NIEHS and Director of the NTP, has advanced similar views on the development of safer and greener products. It is clear that the Glass Fiber Industry has taken a similar view and developed the science to produce and market safer products. This is especially important for products containing glass fiber which are widely used for insulation purposes. The development, production and role of these safer products are fully aligned with national goals for energy conservation and a sustainable "green economy."

4. NTP Expert Panel Evaluation

The NTP's review process for preparation of the 12th RoC (NTP, 2010a) calls for the use of an Expert Panel to provide scientific advice on the listing (or de-listing) of the substances under consideration for listing in the 12th RoC. The NTP Expert Panel, convened in June 2009, was charged (1) to apply the RoC listing criteria to the relevant scientific information and make recommendations regarding its listing status (i.e. *known to be a human carcinogen, reasonably anticipated to be a human carcinogen* or to not list) in the 12th RoC, and (2) to provide a scientific justification for the recommendation. The NTP appointed to the Expert Panel 9 highly qualified scientists with recognized expertise in aerosol science, inhalation toxicology, industrial hygiene, pulmonary medicine, pulmonary biology/pathobiology and hazard evaluation (The members of the NTP Expert Panel are listed in Appendix A).

As background for their deliberations, the NTP Expert Panel was provided a document — "DRAFT, Report on Carcinogens Background Document for Glass Wool Fiber" (NTP, 2009a). The draft document was prepared by SRA International, Inc. under an NIEHS Contract. The NTP Expert Panel also had the benefit of a number of comments submitted by the glass fiber industry. These comments summarized more than two decades of research and hundreds of peer-reviewed publications, largely sponsored by the glass fiber industry (Bauer, 2009; Donaldson, 2009; Hadley and Mentzer, 2004; Hesterberg, 2009; Marsh et al., 2009; Mentzer, 2009 and Ray, 2009). The Expert Panel, at its meeting on June 9-10, 2009, also heard oral presentations from many of these individuals. Undoubtedly, the individual members of the NTP Expert Panel were also knowledgeable of the scientific document prepared to support the IARC separate classifications for Special Purpose and Refractory Ceramic Fibers and Insulation Glass Wool Fibers (IARC, 2002).

The important role of the NTP Expert Panel in assuring the scientific completeness of the information and in recommending listing/de-listing actions on any substance and especially on fiber glass, cannot be over-stated. While the individuals preparing the Background Document (NTP, 2009a), and the NTP staff involved in the activity, were no doubt highly competent scientists, it would be difficult for their credentials to match those of the Expert Panel, the panel members selected by NTP were clearly experts in their relevant fields. It should also be noted that the participants in the NIEHS/NTP Scientific Review Group (NSRG) and Interagency Scientific Review Group (ISRG), that would subsequently participate in the development of the preliminary recommendation on listing/de-listing on glass fiber, were no doubt well-qualified scientists and science administrators. However, it would be unreasonable to expect they would have the same level of scientific expertise as the Expert Panel on each substance, such as glass wool fibers or the specific chemicals, being reviewed for listing (or not listing) in the 12th RoC, as the Expert Panel. Without question, the NTP Glass Wool Fibers Expert Panel is the linch pin element of the RoC process for assuring the scientific validity of any decisions made on listing/de-listing specific categories of glass fibers.

We have independently reviewed the background material including public comments provided to the NTP Expert Panel and the "DRAFT Report on Carcinogens Background Document for Glass Wool Fibers" (NTP, 2009b). It is our professional opinion that the NTP Expert Panel had in hand all of the relevant scientific information for its deliberations on June 9-10, 2009 as a basis for making the recommendations contained in Expert Panel Chairs Reports, Part A and B (Kelsey, 2009a,b).

The recommendations of the NTP Expert Panel with regard to the listing (de-listing) of glass fibers were clear and unambiguous.

- The Expert Panel, by a vote of 8 Yes and 0 No, recommended "that glass wool fibers, with the exception of special fibers of concern (characterized physically below), should not be classified either as *known to be a human carcinogen or reasonably anticipated to be a human carcinogen."*
- The NTP Expert Panel also recommended by a vote of 7 yes, 0 no and 1 abstention, "based on sufficient evidence of carcinogenicity in well-conducted animal inhalation studies, that special purpose glass fibers with the physical characteristics as follows – longer, thinner, less soluble

fibers (for example, ≥ 15 µm length with a K_{dis} of ≤ 100 µg/cm^2/h) –

reasonably anticipated to be human carcinogens for the listing status in the RoC."

By offering two separate and distinct recommendations based on scientific evidence, the NTP Expert Panel was making a statement that it was scientifically inappropriate to continue the practice of lumping all glass fibers together within a single listing as in the 7th RoC and subsequent RoCs. The NTP Expert Panel clearly expressed a scientific opinion that the physical properties and related carcinogenic effects in laboratory animals for certain synthetic fibers, the Special Purpose Fibers, warranted listing these fibers as *"reasonably anticipated to be human carcinogens."* It is equally clear the NTP Expert Panel was of the opinion that scientific evidence supported not listing glass wool fibers as *"reasonably anticipated to be human carcinogens."*

The recommendations of the Expert Panel were subsequently published in the Federal Register by NTP with a request for comments (NTP, August 12, 2009). At least three letters were submitted to the NTP supporting the recommendations of the NTP Expert Panel (Crane, 2009; Ray, 2009; and Venturin, 2009).

5. Comments on Draft Substance Profile

The NTP process (NTP, 2010a) for preparation of the 12th RoC calls for the development of a draft substance profile with a listing recommendation for each candidate substance based on the listing recommendation of the Expert Panel, NSRG and the ISRG and public comments. The recommendations of the NTP Expert Panel, supported by the Public Commentors, are known and publicly available along with the scientific rationale for the recommendations. As noted earlier, the membership of the NSRG and ISRG have not been made known and the results of these deliberations were made in sessions that were not open to the public. It can only be concluded that deference was given to the views of the NTP staff, the NSRG and/or the ISRG in offering a single preliminary recommendation in the "DRAFT Report on Carcinogens Substance Profile for Glass Wool Fibers (Respirable) as a Class" (NTP, 2010b). This preliminary recommendation – "Glass Wool Fibers (Respirable) as a Class, CAS No. None Assigned, Reasonably Anticipated to be a human carcinogen, first listed in the Seventh Annual Report on Carcinogens (1994)" is at odds with the recommendations of the Expert Panel and the public commentors. In proposing to continue a single RoC listing for glass fibers, the DRAFT Substance Profile and embedded preliminary recommendation ignores two decades of new scientific information.

We are pleased to note that the DRART Report explicitly states "This DRAFT substance profile contains the NTP's preliminary recommendations" and "This DRAFT substance profile is distributed solely for the purpose of public comment and dissemination peer review. It should not be construed to represent final NTP determination or policy." We are confident that on further review, the NTP will recognize that its preliminary recommendation was not consistent with current scientific knowledge on different types of glass fibers and their contemporary use and that the NTP should use the listing recommendations of the NTP Expert Panel in proceeding with preparation of the 12th RoC. The action required is preparation of a Substance Profile for "Special Purpose Fibers (Respirable) as a Class – CAS No.: None Assigned, Reasonably anticipated to be a human carcinogen. First listed within a broader class listing in the Seventh Annual Report on Carcinogens (1994)." In addition, a separate brief substance profile needs to be prepared for "Glass Wool Fibers, with the exception of special fibers of concern based on physical characterization – not classified either as known to be a human carcinogen or reasonably anticipated to be a human carcinogen and thus, not listed in the 12th RoC."

The preliminary recommendation for glass wool fibers was apparently reached by considering in aggregate, i.e. lumping together, evidence of carcinogenicity in experimental animals and supporting mechanistic evidence from studies on all kinds of glass fibers. This approach is clearly not justified by the results of the NTP Expert Panel's evaluation of the scientific evidence.

Recall that the Expert Panel determined – "*There is insufficient evidence for carcinogenicity of glass wool in human"* (Kelsey, 2009b). This conclusion was reached based on evaluation of <u>all</u> the epidemiological evidence for all types of glass fibers, irrespective of the specific kind or end use of the fibers. Based on this conclusion, there is no human evidence basis for listing glass fibers of any type as "a human carcinogen" or "reasonably anticipated to be a human carcinogen." Thus, a listing of glass wool fibers or any specific type of fiber glass must be based on consideration of the evidence of carcinogenicity from animal studies or mechanistic considerations.

The NTP Expert Panel reviewed separately as was appropriate, the animal evidence for carcinogenicity of "Glass Wool Fibers (Insulation)" and "Special Purpose Fibers." The NTP Expert Panel concluded there was *"limited evidence of carcinogenicity in animals for insulation glass wool fibers based on an increase in MCL (Mononuclear Cell Leukemia) in one strain of*

rats (F344) from a single study." The Expert Panel's review of the single study mentioned was limited to the summary papers of Mitchell et al. (1986) and Moorman et al. (1988) cited in the "Draft Report on Carcinogens Background Document for Glass Wool Fibers" (NTP 2009a). As we will detail in the next section of this report, we have had the opportunity to review in detail the "Final Report on a Chronic Inhalation Toxicology Study in Monkeys and Rats Exposed to Fibrous Glass," October 25, 1982 (Mitchell et al. 1982), prepared by the Battelle Memorial Institute, Columbus Laboratories, Columbus, OH for the National Institute for Occupational Safety and Health, the sponsors of the research. This report was apparently not available when the SRA International, Inc. and NTP staff prepared the "DRAFT Report on Carcinogens Background Document for Glass Wool Fibers" (NTP, 2009a) and later the "Final Document" (NTP, 2009b), when the NTP Expert Panel met, when the reviews by the NSRG or ISRG were conducted, or when the "DRAFT Report on Carcinogens Substance Profile for Glass Wool Fibers (Respirable) as a Class "was prepared by the NTP staff. Based on our careful review of the detailed report (Mitchell, 1982), it is our professional opinion the Mononuclear Cell Leukemia incidence observed in the single group of F344 rats exposed to Owens Corning glass wool insulation fibers did not represent either statistically significant increase or a biologically significant increase. Indeed, it is apparent that the size distribution of the glass wool insulating fibers to which these rats were exposed was such that the fibers were not respirable and, thus, did not deposit in appreciable quantities in the rat lungs. This is supported by the determination that the lung burdens of glass fibers in the glass wool insulation fiber exposed rats was the same as observed in control rats in the study. We elaborate in detail on the Mononuclear Cell Leukemia issue in the next section of this report.

In our professional opinion, based on the updated analysis of the Mitchell et al. (1982) report, there is no evidence of carcinogenicity in any well-conducted long-term studies of insulation glass wool fibers in rodents. It is our professional opinion that substantial weight should be given to the lack of a carcinogenic response in the well-conducted studies with the MMVF11 and MMVF10 glass wool insulating fibers (Hesterberg et al. 1993). These studies meet contemporary standards for long-term inhalation studies such as those sponsored by the NTP and of the kind we, the authors, were involved in conducting at the Lovelace organization in Albuquerque, NM. Based on our review of all the inhalation studies conducted with glass

wool insulating fibers, we conclude – "There is no evidence for carcinogenicity of glass wool insulating fibers in well-conducted, long-term inhalation studies."

The Expert Panel's report (Kelsey, 2009b) did note a study in which a carcinogenic response was observed in Wistar Rats given large quantities of insulation fibers (B glass) by intraperitoneal injection and a study in which a weak positive response was observed in rats administered insulation glass wool fibers by intrathoracic ingestion. We strongly agree with the Expert Panel's judicious interpretation of these results from studies using non-physiological routes of exposure, especially when these fibers have yielded negative results in well-conducted studies with inhalation exposure, the likely route for human exposures. This view on the importance of giving preference to the results of inhalation studies over results from studies using non-physiological modes of administration has been clearly articulated in the literature (NRC, 2000; Vu et al. 1996; McClellan, 1992; WHO, 1992).

In evaluating the animal evidence for carcinogenicity of Glass Wool Fibers (Special Purpose) the Expert Panel noted "an increased incidence of MCL in F344 rats exposed to Tempstran 100/475. However, there were no increases in lung tumors/mesothelioma in that study." These findings are from the Mitchell et al. (1986) and Moorman et al. (1988) summary papers and should be re-interpreted in light of the information contained in the complete report of Mitchell et al. (1982), which we review in the next section.

Beyond the evidence from human and laboratory animal studies, it is also appropriate to consider the mechanistic information available on various types of glass fibers that has bearing on a determination of the carcinogenic hazard potential for each type of fiber glass. This includes considering mechanistic data on multiple biological endpoints, such as biopersistence, cytotoxicity and genotoxicity. In considering the evidence, it is important to recognize the unique nature of inhaled fiber exposures relative to the more general case of inhaled chemicals.

Fibers represent a special type of inhaled particles. The fraction of airborne fibers measured in the air that can be inhaled is very dependent on the aerodynamic size of the fibers. The aerodynamic size is largely determined by the physical diameter and length and the density of the fibers. The fraction of the inhalable fibers that are subsequently deposited in the various segments of the respiratory tract is also determined by the aerodynamic dimensions of the fibers. The fractions of airborne fibers that are inhaled and deposited for any given aerodynamic size of fiber are very different for laboratory animal species and humans. These differences must be

taken into account in extrapolating the results of any study with implanted or injected fiber or *in vitro* study of the effects of fibers to the inhalation situation. Indeed, it is possible to study *in vitro* or *in vivo* by use of the implantation or injection mode of administering materials, fibers with dimensions such that it is unlikely the fibers could ever be inhaled and deposited by laboratory animals or humans. Moreover, it is easy to administer quantities of fibers to *in vitro* systems or *in vivo* by implantation or injection that substantially exceed the maximum levels that could be studied in inhalation experiments or are likely to ever be experienced by humans.

After fibers are deposited in the respiratory tract, the real dimensions of the fibers, including the surface area as contrasted to aerodynamic size, become the major determinants of fiber clearance and, conversely, retention. In addition, the solubility of the fibers as reflected by the dissolution rate of fibers is a major determinant of the retention of fibers in the body, collectively referred to as biopersistence of fibers. It is now well established that for glass fibers to produce adverse effects when inhaled, the fibers must persist for some time within the respiratory tract. Conversely, if fibers do not persist in the respiratory tract they do not cause adverse effects even when inhaled at high concentrations for long periods of time.

The unique behavior of airborne fibers interacting with the respiratory tract when inhaled is not reproduced in *in vitro* cell or tissue culture assays. Thus, results from such studies need to be extrapolated with extreme caution to the *in vivo* situation with inhaled fibers. Indeed, the results of the *in vitro* assays of cytotoxicity and genotoxicity are of limited utility in predicting the effects of inhaled fibers.

The results for *in vivo* studies in which large numbers of fibers are injected or implanted in the pleural cavity or peritoneal cavity also need to be interpreted with caution as mechanistic evidence for the carcinogenicity of fibers.

It is our professional opinion that the results of *in vitro* cell and tissue studies of genotoxicity and the *in vivo* intra-cavity injection and implantation studies of carcinogenicity should not be interpreted as providing evidence for inhaled glass wool insulation fibers having carcinogenic potential when negative data on carcinogenicity is available from well-conducted inhalation studies.

It is our professional opinion that the mechanistic studies linking the relative rapid dissolution of glass wool insulation fibers with evidence on a lack of carcinogenicity in well-conducted long-term inhalation studies provides strong supporting evidence that is germane to an

overall assessment of the human carcinogenic hazard potential of glass wool insulation fibers. In a similar manner, the mechanistic data linking biopersistence of poorly soluble fibers with carcinogenicity in laboratory animals in well-conducted long-term inhalation studies in rodents must be considered as being highly relevant to an overall assessment of the human carcinogenic hazard potential of poorly soluble fibers, such as some of the special purpose fibers.

The professional opinion we have expressed based on our extensive experience in aerosol science, inhalation toxicology, comparative pathology and the conduct of hazard evaluations mirrors that of the NTP Expert Panel and the earlier IARC Scientific Committee.

The present "Draft RoC Substance Profile for Glass Wool Fibers (Respirable) as a Class" (NTP, 2010b) that treats all glass fibers as a single class does not adequately convey the current status of scientific knowledge on glass fibers and their potential human carcinogenic hazard (or lack of carcinogenic hazard). It is our professional opinion that the NTP should prepare two RoC Substance Profiles that are consistent with the recommendations of the Expert Panel (Kelsey, 2009b). One Substance Profile would be for "Special Purpose Fibers (Respirable) as a Class, CAS No.: none assigned, *Reasonably anticipated to be a human carcinogen*. First listed within a broader listing in the Seventh Annual Report on Carcinogens (1994)." The second Substance Profile would be for "Glass Wool Fibers with exception of special fibers of concern based on physical characterization, CAS No.: none assigned, not classified either as known to be a human carcinogen or reasonably anticipated to be a human carcinogen" and, thus, not listed in the 12th RoC."

6. <u>Over-Interpretation of Mononuclear Cell Leukemia Findings</u>

"The Draft RoC Substance Profile for Glass Wool Fibers (Respirable) as a Class" (NTP, 2010b) makes reference to the published summary papers of Mitchell et al. (1986) and Moorman et al. (1988) as providing evidence for the carcinogenicity of insulation glass fibers. Specifically, on page 3, the Substance Profile states:

"Inhalation exposure of F344 rats to two types of Owens-Corning glass wool (4-6 micron in diameter and >20 microns long of 0.5 to 3.5 microns in diameter and > 10 micron long) significantly increased the incidence of mononuclear cell leukemia (males and females combined), as with the findings for Tempsten code 100/475 glass fibers in this strain (discussed above), these findings were considered to be exposure related (Mitchell et al. 1986, Moorman et al. 1988)".

The NTP's use of this single study as evidence is noteworthy since this is the only evidence cited in the Draft Substance Profile for carcinogenicity from inhaled insulation glass fibers in rodents. Other more recent long-term inhalation studies with glass wool insulating fibers of respirable size, performed to contemporary standards, did not demonstrate carcinogenic effects of any kind including cancers of the respiratory tract which is usually accepted as the target organ for inhaled fibers.

In view of the importance the NTP has attached to the results of this particular study, it was deemed appropriate to locate the original final report for the study (Mitchell et al. (1982) and evaluate the findings that had only been summarized in Mitchell et al. (1986) and Moorman et al. (1988). This study was conducted by the Battelle Memorial Institute's Columbus, OH laboratories under contract to the National Institute of Occupational Safety and Health.

Table 49 from the Mitchell et al. (1982) is reproduced here as Table 1. The original table did not explicitly define the treatment of the specific groups, however, this information is found elsewhere in the report. The original table reported only a statistical evaluation for combined groups of male and female rats. Both of these issues will be addressed in our evaluation.

Table 2 is an expanded version of the original Table 49. The sources of the material used to create the aerosols to which the four groups of "treated" rats were exposed, have now been added as a footnote to Table 2. In addition, as will be discussed in detail later, the results of a statistical evaluation for males and females, separately, is shown.

From Table 2, it is apparent that the Mitchell et al. (1982) study only included one group of rats (Group F01) exposed to a single type of Insulation Fiber Glass, not two types as implied by the quote from the Draft Substance Profile. Groups F02 and F03 were exposed to air filter media and Group F04 to Tempstran Code 100/475, all of which are now defined as Special Purpose Fibers.

The final report (Mitchell et al. 1982) includes details on the methods used to characterize the aerosol exposures. This includes aerodynamic size data obtained using a Cascade Impactor (Figures 20-23) and fiber diameter and length data obtained from analysis of Scanning Electron Microscopic (SEM) images (Tables 19-22). It is not apparent from the Final Report if any measurements were made of samples from the exposure chamber housing the control rats and monkeys or in the holding rooms in which the rats and monkeys were housed

when they were not being exposed. A photograph in the final report shows only four exposure chambers so it is not clear if the control rats and monkeys were sham-exposed in chambers.

The Cascade Impactor Aerodynamic Size data are the most relevant information for estimating the likelihood that the fibers are respirable and likely to reach the pulmonary region of the respiratory tract. The SEM data which are measurements of the physical diameter and length of the fibers provide an indirect measure of the likelihood that the fibers are respirable.

In considering both the aerodynamic size and physical size measurements, it is important to note that the final report indicates the investigators had considerable difficulty in both preparing the material used to generate the Group F01 aerosol and in generating the aerosol. For example, the final report indicates problems with the fibers depositing in the aerosol generation and delivery system. This is not surprising in view of the large diameter and length of the vast majority of the Insulation Glass Fibers (Group F01).

The Cascade Impactor aerodynamic size distribution data for one (Groups F01, F02 and F03) or two days (Group F04) were given in Figures 20-23. One indicator of the likelihood of the aerosol being inhalable is the mass median aerodynamic median (MMAD). The MMAD for the four exposed Groups was as follows: F01 – 4.8 μm, F02 – 6.0 μm, F03 – 5.2 μm and F04 – 1.6 to 1.7 μm. Visual inspection of the graphic data reveals that the aerosols as sampled for Groups F01, F02 and F03 were quite heterodisperse and would have a large geometric size distribution (GSD) if it had been calculated. In contrast, the Group F04 aerosol appeared to have a much smaller GSD. Considering both the estimated MMAD and GSD of the sampled aerosol, it would be anticipated that the aerosol for Group F04 would have a higher likelihood of being respired and deposited in the lungs than the aerosols for Groups F01, F02 and F03.

The measurements of fiber diameter and length made from the SEM images are presented in a three-dimensional array (diameter, length and number of fibers in each diameter/length cell) in Tables 19-22 and in a 3-dimensional array (diameter, length and frequency) in Figures 33-36. For Group F01, there were only a few fibers with physical diameters as small as 3.33 μm and as short as 16.7 μm in length. The vast majority of the fibers had physical diameters greater than 5.0 μm and were greater than 30 μm in length. In contrast, for Groups F02 and F03 there were many fibers with physical diameters of less than 2.0 μm and fiber lengths of 5 to 30 μm. The physical size data for the Group F04 aerosol was strikingly different than that of Groups F01, F-2

Table 1: Reproduced from Mitchell et al. (1982): Table 49

Mononuclear Cell Leukemia (MCL) in the Spleen of Both Early Death and Scheduled Sacrifice Rats

Group	M.C.L. (Males) Total Examined	% M.C.L. Males	M.C.L. (Females) Total Examined	% M.C.L. Females	M.C.L. (Males + Females) Total Examined	% M.C.L. Males + Females
F01	17/50	34.0	20/50	40.0	37/100	37.0*
F02	18/50	36.0	19/50	38.0	37/100	37.0*
F03	20/50	40.0	15/49	30.6	35/99	35.4*
F04	25/50	50.0	17/49	34.7	42/99	42.4**
F05	10/50	20.0	11/49	22.4	21/99	21.2

* $P<0.05$ by Chi s^2 test
** $P<0.01$

Table 2: Correct Statistical Analysis for Mitchell et al. (1982). This is a modification of Table 49, Mononuclear Cell Leukemia (MCL) in the Spleen of Both Early Death and Scheduled Sacrifice Rats

Group	M.C.L. (Males) Total Examined	% M.C.L. Males	M.C.L. (Females) Total Examined	% M.C.L. Females
F01[a]	17/50	34.0	20/50	40.0*
F02[b]	18/50	36.0	19/50	38.0
F03[c]	20/50	40.0*	15/49	30.6
F04[d]	25/50	50.0**	17/49	34.7
F05[e]	10/50	20.0	11/49	22.4

* P<0.05 by Fisher's exact test
** P<0.01 by Fischer's exact test

Group Designations [from page 26 of Mitchell et al. (1982)]

[a]F01 – FG Insulation Fiber Glass,* 4 to 12 micrometer diameter with 4.5 percent binder (red-urea and phenol formaldehyde)
[b]F02 – FM Series Air Filter Media,* 1 micrometer diameter fiber with 12.5 percent binder (yellow-phenol formaldehyde)
[c]F03 – FM Series Air Filter Media,* 1 micrometer diameter fiber without binder
[d]F04 – Tempstran Code 100/475,** 1 micrometer diameter fiber without binder
[e]F05 – Controls

The source materials for Groups F01, F02 and F03 exposures were from Owens-Corning Corporation products and the source material for Group F04 exposure was from a Manville Corporation product.

and F04. Nearly all the fibers were 0.67 μm or less in diameter and 2.0 to 9.7 μm in length. Based on both the aerodynamic size and physical size data, it would be anticipated that only a very small portion, if any, of the fibers to which the F01 rats were exposed would have been respirable.

The Mitchell et al. (1982) report also contains data on the measured lung burden of fibers after 441 to 462 exposure days. Assuming 5 exposures per week, this would yield exposures over a period of 88 to 92 weeks. The lung burden, expressed as number of particles per gram of dry lung, x 10^{-6}, was given in Table J-13. The data as presented were corrected by the authors for background fibers found in the Group F05, control rats. The report states – "Approximately the same number of fibers were found in the control animals as those exposed to the large diameter fibers (F01)." Table J-13 reported 236, 938 and 834 particles per gram of dry lung, x 10^{-6} for Groups F02, F03 and F04, respectively. Thus, the fiber lung burden data confirms the earlier conclusion based on the size distribution of the aerosol to which the rats in Group F01 were exposed – this group exposed to glass wool insulating fiber was essentially a second control group.

Based on the fiber exposure characterization data and the similarity of fiber lung burden in the F01 Group and Control Group rats, the F01 Group in the Mitchell et al. (1982) study would not normally be accepted as providing evidence for or against any exposure-related response. The data clearly indicate the fiber aerosol was not respirable by rats. Moreover, the F01 fibers would have a low probability of being respired and deposited in the respiratory tract of humans. Nonetheless, in as much as NTP included the observation of mononuclear cell leukemia in the Group F01 rats as evidence for carcinogenicity of glass fibers we will review other factors that need to be considered in evaluating that finding.

The spontaneous occurrence of a high incidence of mononuclear cell leukemia (MCL) in F344 rats is well known to inhalation toxicologists, comparative pathologists and others involved in evaluating the potential hazard of exposure to specific chemicals or substances such as inhaled fibers (Solleveld et al. 1984; Haseman et al. 1990; Haseman et al. 1998; Thomas et al. 2007; King-Herbert and Thayer, 2006). Indeed, the occurrence of MCL in F344 rats as a complicating factor in interpreting toxicity/carcinogenicity bioassay was one factor considered in possibly discontinuing the use of the F344 rat as a standard rat strain in the NTP program (King-Herbert and Thayer, 2006).

The specific etiology of MCL in the F344 rat is unknown. Transplantation of the tumor by cell-free lysates, an old approach to evaluating possible viral etiology, has been unsuccessful. There is no definitive evidence of any viral etiology and no reverse transcriptase activity has been found to be associated with MCL. The relatively high incidence of MCL in the F344 strain of rats compared to other rat strains is suggestive of an age-related genetic basis as a probable cause of the disease.

Visual inspection of the incidence of MCL in the five groups (Table 2) in the Mitchell et al. (1982) study reveals a strikingly similar incidence of MCL in both the male and female subgroups within the five groups with the exception of the low incidence in the control males (20% and females (22.4%). The low incidence reported for the male controls in the Mitchell et al. (1982) study contrasts sharply with the F344 rat findings reported by Haseman et al. (1998) from an analysis of the NTP inhalation study control database. Haseman et al. (1998) reported that the average MCL incidence for males was 57.5% (range of 34% to 70%) and for females was 37.3% (range of 24% to 54%). The incidence reported in the four treated groups in the Mitchell et al. (1982) are remarkably similar to the incidence reported by Haseman et al. (1998) for F344 control rats. It should also be noted the rats in the Mitchell et al. study were sacrificed at 27 months of age, and thus the study was of longer duration and the rats were older at terminal sacrifice than for a typical NTP 2-year inhalation study. In summary, it appears not so much that the treated groups in the Mitchell et al. (1982) study have an elevated incidence but that the incidence in the controls group is unusually low.

In view of the high and variable incidence of MCL in the F344 strain of rats, Thomas et al. (2007) have recommended that the statistical criteria given in the FDA Guidance (2001) for statistical aspects of the design, analysis and interpretation of chronic and carcinogenicity studies of pharmaceuticals be used in evaluating potential treatment associated increases in MCL. The FDA guidance is consistent with the views of Lin and Rahman (1998) and Rahman and Lin (2008). The recommendation by Thomas et al. (2007) based on the FDA Guidance (2001) is to use a value $P<0.01$ for a pair-wise comparison and a value $P<0.005$ for a trend test and independently evaluate the effects in male and female rats. That is the approach taken in conducting the statistical evaluations reported in Table 2. This approach contrasts with the approach used by Mitchell et al. (1982), and subsequently reported by Mitchell et al. (1986) and Moorman et al. (1988), in which the statistical evaluation was based on the combined incidence

of MCL in males and females. Using these statistical criteria, only the MCL incidence in males in Group F04 (special purpose fibers) is statistically significant (Table 2). If the incidence values for Groups F02 and F03 are compared to the Group F01 incidence values, the "second control group," there are no statistically significant differences. It is also of interest to compare the incidence of MCL in males in Group F04 to that observed in Group F01, which has noted could be considered as a second control group since the glass wool insulating fibers were not respirable. The MCL incidence in the two groups (F04 vs F01) is not statistically different at the $P<0.01$ level. It can be concluded that even the increased incidence in the Group 4 (Special Purpose Fibers) is not statistically different than that of the controls and, thus, even the MCL effect in that treatment group should be viewed with caution as presumptive evidence of a fiber-related effect. This conclusion does not impact the overall evidence for a carcinogenic effect in laboratory animals for Special Purpose Fibers because there is other evidence for cancers in the respiratory tract.

A final consideration in the MCL issue related to fiber exposure is the lack of biological plausibility. The MCL is generally assumed to originate in the spleen, although the specific etiology is unknown. The spleen is not a target organ from a dosimetric viewpoint even for durable and persistent glass fibers.

Beyond the points made above, it is important to note that the two expert groups, the IARC scientific review committee (IARC, 2002) and the NTP Expert Panel (Kelsey et al. 2009b) were aware of the results originally summarized by Mitchell et al. (1986) and Moorman et al. (1988). Both groups of experts still recommended "limited evidence of carcinogenicity in animals for insulation glass wool fibers." In view of the evidence reviewed above, based on the complete final report of Mitchell et al. (1982), it is our opinion that both expert groups would have likely concluded there is no evidence of carcinogenicity in animals for inhaled glass wool insulation fibers from well-conducted long-term inhalation studies if they had been given the opportunity to review the complete final report (Mitchell et al. 1982) rather than only the summaries published by Mitchell et al. (1986) and Moorman et al. (1988).

7. Conclusions

A large body of new scientific information that is relevant to evaluating the carcinogenic hazard of glass fibers has been published since the NTP listed glass wool fibers as a class in the 7th RoC (NTP, 1994). A critical part of that new information is a series of papers on the results

of extensive epidemiological studies on occupationally exposed cohorts, these studies showed an absence of glass fiber exposure associated cancer. To provide additional insight into the safety of contemporary fiber glass products, industry sponsored a series of long-term inhalation studies in rodents. These studies involved the use of well-characterized fiber aerosols of respirable size and were designed and conducted in accord with the highest contemporary standards for such bioassays including NTP's own standards for inhalation studies. To complement the cancer bioassays, additional mechanistic studies were conducted that have demonstrated the critical importance of fiber durability and biopersistence for glass fibers to produce respiratory disease and cancer. Conversely, glass fibers that are not durable nor biopersistent do not cause respiratory disease or cancer.

Two groups of scientific experts, a total of 28 individuals, knowledgeable of this substantial body of scientific knowledge were convened to evaluate the potential carcinogenic hazards of inhaled glass fibers. The first group of 19 scientists was convened by IARC (2002) and concluded there was a sound scientific basis for providing separate evaluations for (a) special purpose fibers, (b) refractory ceramic fibers, and (c) insulation glass wool fibers. The Summary Evaluation and Overall Evaluation of the IARC Committee are given in Appendix A. In consideration of the IARC (2002) recommendations, the North American Insulation Fiber Association petitioned the NTP to review its listing of glass fibers as part of the process of preparing the 12th RoC.

The NTP appointed a 9 person panel of scientific experts on glass fibers to review the scientific evidence on glass fiber carcinogenicity and make recommendations for the listing of glass fibers in the 12th RoC. The Panel's review was facilitated by the availability of the Draft RoC Background Document for Glass Wool Fibers (NTP, 2009a) and receipt of numerous written comments from the glass fiber industry that focused on the new scientific evidence developed since the earlier review that led to the listing of Glass Wool Fibers (Respirable) as a Class in the 7th RoC (NTP, 1994).

The NTP Glass Wool Fiber Expert Panel's recommendations (Kelsey, 2009b) are remarkably similar to those of the earlier IARC Scientific Committee (IARC, 2002). The NTP Expert Panel concluded:

(1) "*There is insufficient evidence for the carcinogenicity of glass wool in humans.*"

(2) *There is "limited evidence of carcinogenicity in animals for insulation glass wool fibers based on an increase in MCL in one strain of rats (F344) from a single study."*

(3) *There is "sufficient evidence for carcinogenicity in animals administered special purpose glass fibers based on positive studies in rats and hamsters by the inhalation route."*

Based on these science-based conclusions, the Expert Panel made two specific recommendations. First, the Panel recommended by a vote of 8 yes/0 no "that glass wool fibers, with the exception of special fibers of concern (characterized physically below) should not be classified either as known to be a human carcinogen or reasonably anticipated to be a human carcinogen." Second, the Expert Panel, by a vote of 7 yes/0 no/1 abstention recommended – "based on sufficient evidence of carcinogenicity in well-conducted animal inhalation studies, that special purpose glass fibers with the physical characteristics as follows – longer, thinner, less soluble fibers (for example, $\geq$ 15 μm length with a K_{dis} of < 100 ng/cm^2/h) – *reasonably anticipated to be a human carcinogen for the listing status in the RoC.*

We strongly concur in the conclusions and recommendations of the NTP Expert Panel and the earlier IARC Committee, concurrence that is based on our extensive experience in inhalation toxicology, comparative pathology and human cancer hazard evaluation. We have carefully reviewed the "Draft RoC Substance Profile for Glass Wool Fibers (Respirable) as a Class" and cannot find any scientific basis within that document for disregarding the expert advice NTP received. The NTP has not provided a scientific rationale for the preliminary recommendation that treats glass fibers as a single class. We urge the NTP Board of Scientific Counselors to recommend to the NTP that it follow the scientific advice it has received and prepare two separate Substance Profiles, one for Special Purpose Fibers – *reasonably anticipated to be human carcinogens*, for listing in the 12th RoC and a second Substance Profile for Glass Wool Insulation Fibers – not classified as known to be a human carcinogen or reasonably anticipated to be a human carcinogen to replace the current listing included in the 7th RoC.

It is important to recognize that the conclusions on potential human carcinogenic hazard of all glass fibers are grounded in an extensive body of epidemiological observations that the IARC Expert Committee concluded, provided inadequate evidence in humans for carcinogenicity of glass wool, continuous glass filament, and refractory ceramic fibers and, the NTP Expert Panel concluded – there is insufficient evidence for carcinogenicity of glass wool in humans. Thus, the separate recommendations for the two types of glass fibers should be based

on the results of well-conducted, long-term inhalation studies in rodents and mechanistic data. Those data clearly support separate recommendations for (a) glass wool fibers -- not classified as *a human carcinogen or reasonably anticipated to be a human carcinogen* and (b) Special Purpose Fibers – *reasonably anticipated to be human carcinogens* using NTP classification criteria.

8. Declaration of Interest

McClellan has provided scientific advice for over 25 years to both public agencies and private industry on health issues related to man-made fibers, in some instances he was compensated for professional services while the vast majority of his effort was provided without compensation. Hahn has provided professional advice on the pathological effects of inhaled particulate material, including fibers, to both public and private organizations, in his role as a staff scientist while employed at the Lovelace organization. Hahn has previously conducted fiber dissolution studies under contract to the North American Insulation Manufacturers Association (NAIMA). McClellan and Hahn have been engaged by the NAIMA to review and comment on the "Draft Substance Profile for Glass Wool Fibers (Respirable) as a Class." However, the opinions expressed in this document are the independent professional views of McClellan and Hahn, and may not necessarily represent the views of the NAIMA.

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10. Appendix A

a. NTP Glass Wool Fibers Expert Panel Membership

The Report on Carcinogens (RoC) expert panel for glass wool fibers exposures met at the Sheraton Chapel Hill Hotel, Chapel Hill, North Carolina on June 9-10, 2009 to peer review the draft background document on glass wool fibers exposures and make a recommendation for listing status in the 12th Edition of the RoC.

Members of the expert panel are as follows:

Karl Kelsey, M.D., M.O.H., Chair
Department of Pathobiology and
Laboratory Medicine
Brown University

Aaron Blair, Ph.D., M.P.H.
Occupational & Environmental
Epidemiology Division of Cancer
Epidemiology & Genetics
National Cancer Institute

Michael Elwell, Ph.D., D.V.M.
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Covance Laboratories

Andrij Holian, Ph.D.
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b. IARC Synthetic Vitreous Fiber Expert Committee Membership (IARC, 2002) Lyon, 9-16 October 2001

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c. IARC Expert Panels Evaluation of Synthetic Vitreous Fibers (from IARC, 2002)

1. Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of glass wool.

There is *inadequate evidence* in humans for the carcinogenicity of continuous glass filament.

There is *inadequate evidence* in humans for the carcinogenicity of rock (stone) wool/slag wool.

There is *inadequate evidence* in humans for the carcinogenicity of refractory ceramic fibres.

There is *sufficient evidence* in experimental animals for the carcinogenicity of special-purpose glass fibres including E-glass and '475' glass fibres.

There is sufficient evidence in experimental animals for the carcinogenicity of refractory ceramic fibres.

There is *limited evidence* in experimental animals for the carcinogenicity of insulation glass wool.

There is *limited evidence* in experimental animals for the carcinogenicity of rock (stone) wool.

There is *limited evidence* in experimental animals for the carcinogenicity of slag wool.

There is *limited evidence* in experimental animals for the carcinogenicity of certain newly developed, more biopersistent fibres including fibre H.

There is inadequate evidence in experimental animals for the carcinogenicity of continuous glass filament.

There is *inadequate evidence* in experimental animals for the carcinogenicity of certain newly developed, less biopersistent fibres including the alkaline earth silicate (X-607) wool, the high-alumina, low-silica (HT) wool and fibres A, C, F and G.

2. Overall Evaluation

Special-purpose glass fibres such as E-glass and '475' glass fibres are *possibly carcinogenic to humans* (Group 2B)

Refractory ceramic fibres are *possibly carcinogenic* to humans (Group 2B)

Insulation glass wool, continuous glass filament, rock (stone) wool and slag wool are *not classifiable as to their carcinogenicity to humans* (Group 3)

The Working Group elected not to make an overall evaluation of the newly developed fibres designed to be less biopersistent such as the alkaline earth silicate or high-alumina, low-silica wools. This decision was made in part because no human data were available, although such fibres that have been tested appear to have low carcinogenic potential in experimental animals, and because the Working Group had difficulty in categorizing these fibres into meaningful groups based on chemical composition.

APPENDIX B - Biographies

a. Roger O. McClellan, DVM, MMS, DSc (Honorary), Diplomate-ABT, Diplomate-ABVT, Fellow-ATS
Advisor, Toxicology and Human Health Risk Analysis
Albuquerque, NM 87111-7168

Roger O. McClellan is currently an advisor to public and private organizations on inhalation toxicology and human health risk analysis issues. He received a Doctor of Veterinary Medicine degree with Highest Honors from Washington State University (1960). He is a Diplomate of the American Board of Toxicology and the American Board of Veterinary Toxicology and a Fellow of the Academy of Toxicological Sciences, American Association for Advancement of Science, Society for Risk Analysis and American Association for Aerosol Research.

He is an internationally recognized authority in the fields of inhalation toxicology, aerosol science and human health risk analysis. He is also well known for the leadership he provided to the Lovelace Inhalation Toxicology Research Institute (1966-1988) in Albuquerque, NM and the Chemical Industry Institute of Toxicology (1988-1999) in Research Triangle Park, NC. Both organizations are internationally recognized for their research on the mechanisms of action of pollutants and assessing human health risks. He has authored over 300 scientific papers and reports and edited 10 books. He frequently speaks on risk assessment and air pollution issues in the United States and abroad. He is a Past President of the Society of Toxicology and the American Association for Aerosol Research. He serves in an editorial role for a number of journals, including continuing service as Editor of Critical Reviews in Toxicology. He serves or has served on the Adjunct Faculty of 8 universities.

McClellan has served in an advisory role to numerous public and private organizations including service on senior advisory committees for 8 federal agencies and on many committees of the National Academy of Sciences/National Research Council. He is past Chairman of EPA's Clean Air Scientific Advisory Committee and served on Panels that have reviewed the National Ambient Air Quality Standards for all of the Criteria Pollutants.

McClellan's contributions have been recognized by receipt of a number of honors. He was elected in 1990 to membership in the Institute of Medicine of the National Academy of Sciences. He received the Society of Toxicology Merit Award and Founders Award and the New Mexico Distinguished Public Service Award. In 2005, The Ohio State University awarded him an Honorary Doctor of Science degree for his contributions to the science under-girding improved air quality. In 2008, Washington State University presented him the Regents Distinguished Alumnus Award, the highest recognition the University can bestow on an alumnus. He is a strong advocate of risk-based decision-making integrating information from epidemiological studies, clinical investigation, laboratory animal bioassays and mechanistic studies using molecules, cells, tissues and intact mammals.

b. Fletcher F. Hahn, BS, DVM, DACVP
Hahn Consulting
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Dr. Fletcher Hahn is a Diplomate of the American College of Veterinary Pathologists, a certification he has held since 1971. He was granted a DVM from Washington State University in 1964, served in the US Army for 2 years at the Walter Reed Army Institute of Research and earned a PhD in Comparative Pathology at University of California, Davis, in 1971. He worked as a toxicologic pathologist at the Lovelace Respiratory Research Institute, Albuquerque, NM, from 1971 to 2004. Since retirement, he has consulted in the field of toxicologic pathology with special interest in reactions of the lung to injury.

Dr. Hahn's primary interest is in the health effects of inhaled environmental contaminants, using exposed animals to determine possible effects in man. As a principal investigator and collaborator, he has studied the morphologic changes and the pathogenesis of diseases resulting from materials inhaled by laboratory animals. The focus has been on pulmonary inflammation, fibrosis and neoplasia that result from inhaled chemical vapors, oxidant gases, wood and cigarette smoke, metallic particles, fibers and radioactive materials (e.g. Ce, Pu, and DU). Extrapolation of results from animals to man is a focus as exemplified by a recent comparison of the pulmonary reactions of man and rats to inhaled dusts and the distribution of particles in the lungs of plutonium workers.

Dr. Hahn has also been study pathologist on numerous studies conducted using GLP procedures. These include carcinogenicity bioassays of inhaled talc, nickel subsulfide, nickel oxide, and nickel sulfate conducted for the National Toxicology Program. Also included are safety studies of bronchial thermoplasty for treatment of asthma, laser diodes for treatment of benign prostatic hypertrophy, IL 12 combined with radiation for cancer therapy, inhaled hormones, inhaled polyacrylics and inhaled gene therapy vectors. He has also served on numerous pathology review panels in the area of inhalation toxicology. He has authored or co-authored over 270 open literature publications, primarily in these areas of interest.